Re: Determinants of BRAF Mutations in Primary Melanomas

I read with interest the paper by Maldonado et al. *(1)* investigating the distribution of BRAF mutations across different melanoma types. One of the questions addressed by the authors was whether cutaneous melanomas with a BRAF mutation arose from preexisting melanocytic nevi. In an analysis of 46 lesions, they found melanomas with an associated nevus to have only a slightly higher prevalence of BRAF mutation (55%; n = 11) than did melanomas exhibiting no evidence of nevus (43%; n = 35); the difference was not statistically significant. On the basis of these findings, the authors concluded that not all melanomas with an associated nevus may arise from melanocytes with BRAF mutations.

When one is assessing melanomas for histologic evidence of a preexisting nevus, thick tumors are not necessarily informative, given the possibility that evidence of a preexisting nevus may have been obliterated by the growing tumor *(2)*. The misclassification of tumors with respect to evidence of a preexisting nevus would be expected to attenuate or obscure actual differences in tumor characteristics between melanomas that arise from a precursor nevus and melanomas that arise de novo. The level of misclassification in the study of Maldonado et al. may be fairly high, given that the cutaneous melanomas included in their analysis were relatively thick (median thickness = 3.6 mm; range = 1–15 mm).

It would be informative if the authors addressed this issue by restricting their analytic sample to thinner melanomas to minimize the effects of such misclassification. In addition, it may be advisable to exclude acral lentiginous melanomas from the analysis, because the etiology of this tumor subtype appears to be quite different from that of other cutaneous melanomas *(3)*.

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References

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Note

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RESPONSE

We respond with interest to Dr. Purdue's commentary raising two important issues about our observation that not all melanomas with an associated nevus arise from melanocytes with BRAF mutations. He correctly points out that we could have missed preexisting nevi in some of our melanomas, because the melanomas included in our analysis were relatively thick and, therefore, could have overgrown a nevus that was present earlier in the evolution of the tumor. To address this point, he suggested reanalyzing the data by excluding thicker tumors and by excluding melanomas from acral skin.

We would like to clarify that our original analysis, in which we compared the BRAF mutation frequencies for melanomas with and without a microscopically detectable nevus contiguous with the melanoma, was restricted to the groups with chronic sun damage and no chronic sun damage and, thus, already excluded acral and mucosal melanomas. In this analysis, we had found that only six of 11 melanomas with an associated nevus had BRAF mutations in the melanoma portion. Our conclusion that "not all melanomas with an associated nevus may arise from melanocytes with BRAF mutations" thus was based on the melanomas in which we in fact did observe an associated nevus; our conclusion was not based on the melanomas in which we did not find a nevus and, therefore, could have missed one.

However, we fully acknowledge that, because our melanomas were relatively thick (mean thickness = 3.6 mm), some melanomas in which we did not observe an associated nevus may have had such a nevus earlier in their progression that had later been overgrown. To address this point in more detail, we further excluded melanomas with evidence of chronic sun damage because these melanomas typically also do not arise from preexisting nevi. First, we examined melanomas in the group with no chronic sun damage to determine whether those without an associated nevus were thicker than those with an associated nevus. If melanomas without a detectable nevus were thicker than melanomas with a nevus, we could have missed some nevi in this group. Specifically, we compared the frequency of associated nevi in melanomas thinner than 3.6 mm with that in melanomas thicker than or equal to 3.6 mm. We included 32 melanomas from the no-chronic- sun-damage group in this analysis; 11 melanomas were excluded because the specimen did not allow full assessment for an associated nevus or because information regarding depth was not available. The threshold of 3.6 mm was as described by Sagebiel *(1)*. Ten of the 32 melanomas had an associated nevus; six of these 10 melanomas were thinner than 3.6 mm, and four were thicker. By contrast, 22 of the 32 melanomas were not associated with a nevus; 11 of these 22 melanomas were thinner than 3.6 mm, and 11 were thicker ($P = .71$ by Fisher's exact test; alternatively, $P = .79$ by the Wilcoxon rank sum test). All statistical tests were two-sided. Thus, we found no evidence that melanomas without a nevus were thicker than melanomas with a nevus. Consequently, we suggest that it is unlikely that nevi were missed with appreciable frequency in thicker melanomas.

We also restricted the analysis of the frequency of BRAF mutations to melanomas with no chronic sun damage that were thinner than 3.6 mm. In this group, the likelihood of missing an associated nevus is considered lower than in melanomas that are thicker *(1)*. We found that three of six melanomas with an associated nevus did have a BRAF mutation compared with seven of 11 melanomas without an associated nevus ($P = .64$, Fisher's exact test). Although the number of melanomas examined in our study was far too low to definitively answer this question, our results suggest that, on intermittently sun-exposed skin, melanomas that do arise from nevi do not have more frequent BRAF mutations than melanomas that do not arise from nevi.

Thus, our original hypothesis that not all melanomas arising within an associated nevus have BRAF mutations is supported by our data. We did not find evidence that we had missed nevi in thick melanomas.

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Reference

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Notes

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